Progesterone for the prevention of preterm birth in twin pregnancy (STOPPIT)

Progesterone for the prevention of preterm birth in twin pregnancy (STOPPIT): a randomised, double-blind, placebo-controlled study and meta-analysis

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Summary

Background Women with twin pregnancy are at high risk for spontaneous preterm delivery. Progesterone seems to be effective in reducing preterm birth in selected high-risk singleton pregnancies, albeit with no significant reduction in perinatal mortality and little evidence of neonatal benefit. We investigated the use of progesterone for prevention of preterm birth in twin pregnancy.

Methods In this double-blind, placebo-controlled trial, 500 women with twin pregnancy were recruited from nine UK National Health Service clinics specialising in the management of twin pregnancy. Women were randomised, by permuted blocks of randomly mixed sizes, either to daily vaginal progesterone gel 90 mg (n=250) or to placebo gel (n=250) for 10 weeks from 24 weeks' gestation. All study personnel and participants were masked to treatment assignment for the duration of the study. The primary outcome was delivery or intrauterine death before 34 weeks' gestation. Analysis was by intention to treat. Additionally we undertook a meta-analysis of published and unpublished data to establish the efficacy of progesterone in prevention of early (<34 weeks' gestation) preterm birth or intrauterine death in women with twin pregnancy. This study is registered, number ISRCTN35782581.

Findings Three participants in each group were lost to follow-up, leaving 247 analysed per group. The combined proportion of intrauterine death or delivery before 34 weeks of pregnancy was 24·7% (61/247) in the progesterone group and 19·4% (48/247) in the placebo group (odds ratio [OR] 1·36, 95% CI 0·89–2·09; p=0·16). The rate of adverse events did not differ between the two groups. The meta-analysis confirmed that progesterone does not prevent early preterm birth in women with twin pregnancy (pooled OR 1·16, 95% CI 0·89–1·51).

Interpretation Progesterone, administered vaginally, does not prevent preterm birth in women with twin pregnancy.

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Introduction

Multiple pregnancies accounted for 1·6% of all births in the UK during 2007,[1,2] with more than 98% of these multiple births being twin births.[2] Rates of stillbirth and neonatal mortality for multiple pregnancies are 14·9 and 19·8 per 1000 livebirths, respectively, and are three to eight times higher than for singleton pregnancies.[3] The economic costs of health-care provision in the first 5 years of life are twice as high per child after twin birth compared with singleton birth.[4]

Prematurity continues to be the major cause of neonatal death in multiple births, with preterm labour potentially the most treatable cause of prematurity.[3] In the long term, the morbidity in both singleton and multiple survivors of preterm birth is well documented, and is known to lead to poor health and reduced achievement both in school and in adulthood.[5] Such morbidity is associated with major financial costs to the health service, and with personal suffering to the individuals and their families.

No effective interventions have been shown to prevent preterm delivery in twin pregnancy. By contrast, three large randomised trials[6–8] have suggested that progesterone might prevent preterm delivery in high-risk singleton pregnancy. The likelihood of preterm birth in women with singleton pregnancy who are identified at risk of preterm delivery because of either a previous preterm delivery[6,7] or a short cervix[8] might be reduced by antenatal progesterone. Importantly, evidence that a reduction in the rate of preterm birth is accompanied by neonatal benefit is scarce because there is no reduction in perinatal mortality, and risk of neonatal sepsis is the only secondary neonatal outcome that is reduced in babies of women with singleton pregnancy treated with antenatal progesterone.[9]

The STOPPIT study (STudy Of Progesterone for the Prevention of Preterm Birth In Twins) was designed to test the hypothesis that the occurrence of delivery or intrauterine death before 34 weeks and 0 days of gestation would be lower in women with twin pregnancy randomly assigned to progesterone gel than in those randomly assigned to matching placebo.

Methods

Participants

Women were recruited between Dec 1, 2004, and April 30, 2008 from specialised antenatal clinics caring for women

with multiple pregnancy at nine UK National Health Service hospitals. All women with a twin pregnancy, with gestation and chorionicity established by scan before 20 weeks' gestation, and attending the antenatal clinic during the recruitment period were eligible for recruitment. Women were not eligible if their pregnancy was complicated by a recognised structural or chromosomal fetal abnormality at the time of recruitment, or if they had contraindications to progesterone, planned cervical suture, planned elective delivery before 34 weeks' gestation, or planned intervention for twin-to-twin transfusion before 22 weeks' gestation. Women with higher multiple pregnancy were also excluded.

Participants gave written informed consent, and the study was granted approval by the West Glasgow Ethics Committee 1 (reference 04/S0703/13).

Procedures

We aimed to recruit and randomly assign women at 22 weeks' gestation. When possible, the project was discussed with women at booking, and again at 22 weeks' gestation. All women had at least 1 week to decide whether to participate. Participants were randomly assigned to either daily progesterone gel (90 mg; Crinone [Serono, Feltham, Middlesex, UK]) or to placebo gel administered vaginally by the participant and starting at 24 weeks and 0 days of gestation. Drugs were supplied in a sealed opaque covering. Every cover contained a single-use, one piece, white polyethylene applicator with a twist-off top, designed for intravaginal self-insertion. Each applicator contained 1·45 g of gel and delivered 1·125 g of gel, containing either 8% progesterone or excipients (glycerin, light liquid paraffin, hydrogenated palm oil glyceride, carbopol 974P, sorbic acid, polycarbophil, sodium hydroxide, and purified water).

We used a randomisation schedule with permuted blocks of randomly mixed sizes to make up treatment packs (either active or placebo) for every patient, which were held in individual hospital pharmacies until use. On recruitment, the local researcher (usually a midwife) telephoned the interactive voice response randomisation application at the UK Clinical Research Network registered trials unit (The Centre for Healthcare Randomised Trials [CHaRT], in the Health Services Research Unit, University of Aberdeen, UK), to be given a participant number that corresponded to a specific treatment pack. We used a minimisation algorithm incorporating hospital and chorionicity to assign participants to the randomised treatment group.

All study personnel and participants were masked to treatment assignment for the duration of the study. Only the study statistician and the independent Data Monitoring Committee had access to unblinded data, but none had any contact with study participants.

Outcomes

The primary outcome was delivery or intrauterine death before 34 weeks and 0 days of gestation. We used delivery of the first twin to define the time of delivery. If one twin died in utero before 34 weeks and the other was born alive after 34 weeks, intrauterine fetal death was defined as occurring before 34 weeks. The gestational age was calculated from ultrasound scan done before 20 weeks. The maternal secondary outcomes were gestation at delivery, method of delivery (spontaneous vaginal delivery, vaginal breech, forceps or ventouse, or caesarean section), duration of each stage of labour, and safety outcomes such as duration of stay in hospital. Neonatal secondary outcomes were neonatal unit admission and duration of neonatal unit care. We also ascertained maternal satisfaction by questionnaire. Women were followed up from randomisation until they gave birth. Outcomes were recorded from the hospital notes, and entered into a web-based data capture system by a trained clinician, usually a study midwife.

Statistical analysis

The proportion of deliveries before 34 weeks' gestation in twin pregnancy is about 20% (Chalmers J, Information Services Division, NHS Scotland, Edinburgh, UK, personal communication). Our study size of 250 women per group gave 85% power at 5% significance level to show a reduction in the rate of preterm delivery or intrauterine death before 34 weeks' gestation from 20% to 10% in the active treatment group and was based on a conservative estimate of likely effect size derived from previous studies.[6,7]

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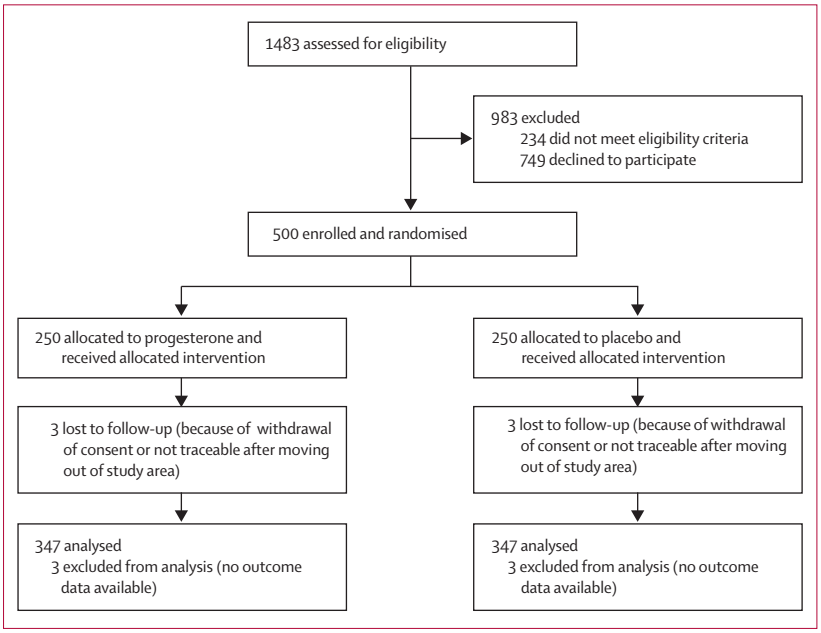

Figure 1: **Trial profile**

Analysis was done by intention to treat and followed a prespecified statistical analysis plan. For the primary outcome, the odds ratio (OR) of the treatment effect, adjusting for the minimisation covariate (chorionicity), was estimated with a 95% CI, and associated likelihood ratio p value with logistic regression. We also undertook a predefined subgroup analysis of the primary outcome by monochorionicity (yes or no). We analysed continuous maternal secondary outcomes with normal linear regression models, adjusting for chorionicity. Treatment effects, 95% CIs, and p values were calculated as described in the statistical analysis plan. We analysed binary categorical secondary outcomes with logistic regression as per the primary outcome. For data with multiple categories (eg, method of delivery), we compared the two randomised groups with a proportional odds model.

Fetal outcomes allowed for the clustering within twins. Analyses were as for the maternal outcomes, except with the addition of mother as a random effect in the linear and logistic regression models. No missing data were imputed. No adjustment was made for any multiple comparisons. An independent Data Monitoring Committee met regularly throughout the study. No formal interim analyses were undertaken, and so no adjustment was made. All statistical analyses were undertaken in SPSS for Windows (version 17.0.0) and Stata (version 10.1).

The trial was registered on EUDRAct, number 2004-000780-10, and as an International Standard Randomised Controlled Trial, number ISRCTN35782581.

	Progesterone (n=250)	Placebo (n=250)
Demographics and lifestyle		
Mean age (years [SD; min–max])	33 (5; 18–44)	33 (6; 19–50)
Current smoking	44 (18%)	31 (12%)
Current alcohol	179 (72%)	177 (71%)
Obstetric history		
Parity (>0)	119 (48%)	122 (49%)
Miscarriage (>0)	3 (1%)	1 (<1%)
Medical disorders		
Hypertension	3 (1%)	1 (<1%)
Insulin-dependent diabetes	1 (<1%)	1 (<1%)
Respiratory disease	8 (3%)	17 (7%)
Cardiac disease	2 (1%)	1 (<1%)
Neurological disease	0	1 (<1%)
Skin condition	4 (2%)	8 (3%)
Thrombophilia	2 (1%)	2 (1%)
Current pregnancy		
Fetal anomaly scan: twin 1		
Normal	242 (97%)	243 (97%)
Defined abnormality	3 (1%)	1 (<1%)
Uncertain abnormality	0	0
Not done	5 (2%)	6 (2%)
Fetal anomaly scan: twin 2		
Normal	242 (97%)	242 (97%)
Defined abnormality	3 (1%)	2 (1%)
Uncertain abnormality	0	0
Not done	5 (2%)	6 (2%)
Amniocentesis for twin 1 abnormal	0	0
Amniocentesis for twin 2 abnormal	0	0
CVS done	1 (<1%)	0

Data are number (%) unless otherwise indicated. CVS=chorionic villus sampling.

Table 1: **Baseline characteristics**

	Progesterone		Placebo		Odds ratio progesterone *vs* placebo (95% CI)	p value
	n	Event (%)	n	Event (%)		
All pregnancies	247	61 (24·7%)	247	48 (19·4%)	1·36 (0·89–2·09)	0·16*
Monochorionic pregnancies	46	10 (21·7%)	45	14 (31·1%)	0·62 (0·24–1·58)	..
Dichorionic pregnancies	201	51 (25·4%)	202	34 (16·8%)	1·73 (1·06–2·83)	..

*Refers to p value for proportion in progesterone versus placebo group (from a logistic regression model adjusting for chorionicity). For test of interaction between monochorionic and dichorionic pregnancies, p=0·056.

Table 2: **Primary outcome (proportion of women delivering or with intrauterine death before 34 weeks) overall and by subgroup of chorionicity**

Meta-analysis

We did an electronic search of the published medical literature (PubMed and Cochrane Controlled Trials Register) for studies in which women with twin pregnancy were randomly allocated to treatment with a progestogen (including progesterone, 17-hydroxy-progesterone caproate) or placebo in the second or third trimester with the intention to prevent preterm birth. We used the search terms "preterm birth" AND ["progesterone" OR "17 hydroxyprogesterone caproate" OR "progestogen"] AND ["pregnancy multiple" OR "pregnancy twin"] AND "randomised controlled trial" AND "human". We considered all published randomised controlled trials in which progestogens were given to women with twin pregnancy for the prevention of preterm birth. We excluded those in which progestogens were given to women with symptoms of preterm labour, or in which data were available in abstract form only. Two reviewers (J E Norman and J Norrie) reviewed identified papers for relevance and quality, and abstracted the data. Published studies were assessed for quality according to Jadad's quality assessment scale.[10]

Our prespecified primary outcomes were the incidence of delivery or intrauterine fetal death before 34 weeks' gestation. When data for our primary outcome of interest were not available in the published report, we contacted the relevant chief investigator to obtain the required information. We calculated ORs and 95% CIs for the primary outcome.

Role of the funding source

Neither the funder nor the supplier of active and placebo drugs had any role in study design, data collection, data

analysis, data interpretation, or writing of the report. The joint study sponsor in terms of the EU Clinical Directive had no role in analysis of data. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Figure 1 shows the trial profile. Participants attended clinic visits at the time of randomisation (baseline) and at intervals during pregnancy, and were admitted to the study hospital for delivery and postnatal care.

Table 1 shows the baseline demographics and clinical characteristics of the participants. Three women in each of the progesterone and the placebo groups were lost to follow-up (because of withdrawal of consent or not traceable after moving out of study area); thus data from 494 patients were available for the intention-to-treat analysis of the primary outcome. No patients were considered protocol violators, and none were unblinded before ascertainment of all outcomes. Thus 494 mothers and 988 babies remained for the per-protocol analyses.

The proportion of women delivering or with an intrauterine death before 34 weeks was 61/247 (24·7%) in the progesterone group and 48/247 (19·4%) in the placebo group (OR 1·36 [95% CI 0·89–2·09], p=0·16; table 2). Thus, by contrast with our original hypothesis, progesterone did not reduce the incidence of preterm delivery or intrauterine death before 34 weeks' gestation. Subgroup analysis of the primary outcome by chorionicity suggested an increase in the rate of preterm delivery or intrauterine death before 34 weeks in association with progesterone in women with dichorionic pregnancies (table 2). However, the p value for the formal test of interaction between the monochorionic and dichorionic groups was not significant (p=0·056), implying that the response to treatment in the monochorionic and dichorionic groups did not differ significantly. Thus the finding of increased rates of adverse outcomes in the dichorionic group should be interpreted with suitable caution.

Tables 3 and 4 show secondary maternal outcomes, table 5 neonatal outcomes, table 6 safety issues, table 7 side-effects, and table 8 maternal satisfaction. The only apparent differences between the groups were reduced odds of caesarean (OR 0·53, 95% CI 0·34–0·84; p=0·006), operative vaginal delivery (OR 0·42, 0·21–0·83; p=0·013), and nausea (OR 0·43, 0·20–0·94; p=0·035) in the progesterone group. The rate of adverse events did not differ between the two groups (table 6).

136 women in the progesterone group and 151 women in the placebo group returned diaries indicating that they had taken 80% or more of their medication. The remainder either did not return their diary or stopped early because of preterm delivery, because they were told to stop, or because they were incompletely compliant with treatment.

	Progesterone		Placebo		Mean difference (95% CI)	p value
	n	Mean (SD)	n	Mean (SD)		
Gestational age birth (weeks)	247	35·4 (3·5)	247	35·7 (3)	−0·3 (−0·9 to 0·3)	0·31
Duration of labour stage 1 (min)*	82	327 (284)	63	360 (380)	−33 (−142 to 75)	0·55
Duration of labour stage 2 (min)*	82	102 (94)	63	116 (91)	−14 (−45 to 17)	0·36
Duration of labour stage 3 (min)*	82	19 (28)	63	16 (29)	3 (−6 to 12)	0·53
Duration of labour overall (min)*	82	447 (327)	63	496 (418)	−48 (−171 to 74)	0·44

*Vaginal deliveries only.

Table 3: **Gestational age at birth and duration of labour (secondary outcomes)**

	Progesterone		Placebo		Odds ratio progesterone *vs* placebo (95% CI)	p value
	n	Event (%)	n	Event (%)		
Not recorded	250	14 (5·6%)	250	21 (8·4%)	..	..
LSCS	250	148 (59·2%)	250	161 (64·4%)	0·53 (0·34–0·84)	0·006
Forceps or ventouse	250	22 (8·8%)	250	30 (12·0%)	0·42 (0·21–0·83)	0·013
SVD or vaginal breech	250	66 (26·4%)	250	38 (15·2%)	1·00	1·00

LSCS=lower-segment caesarean section. SVD=spontaneous vertex delivery.

Table 4: **Method of delivery (hierarchical; secondary outcome)**

	Progesterone		Placebo		Odds ratio progesterone *vs* placebo or mean difference (95% CI)†	p value
	n	Event (%) or mean (SD)*	n	Event (%) or mean (SD)*		
Admission to neonatal unit	494	167 (33·8%)	494	158 (32·0%)	1·08 (0·76 to 1·54)	0·65
Duration of neonatal unit stay: all babies (days)	494	7·5 (19·9)	494	8·7 (23·1)	1·5 (−1·9 to 5·0)	0·38
Duration of neonatal unit stay: only babies admitted to neonatal unit (days)	167	26·9 (33·5)	158	23·6 (29·5)	3·3 (−5·3 to 11·9)	0·45

These data refer to all twins, both the first and second, with 95% CIs and p values adjusted for clustering among the twin set. *Data are event (%) for admission to neonatal unit, and mean (SD) for duration of neonatal unit stay. †Data are odds ratio (95% CI) for progesterone versus placebo for admission to neonatal unit, and mean difference (95% CI) for duration of neonatal unit stay.

Table 5: **Neonatal complications (secondary outcomes)**

Electronic searching of published work generated 198 results relevant for meta-analysis. Review of the abstracts indicated that only two studies fulfilled the inclusion criteria. Relevant data could be abstracted from one of these papers.[11] In view of the discrepancy between the published primary outcome (spontaneous preterm delivery before 34 weeks' gestation) and the outcome we planned for the meta-analysis (intrauterine death or any preterm delivery before 34 weeks' gestation) we contacted the senior author of the other paper[8] who supplied the relevant data. A further paper[12] was not found on electronic searching, but was brought to the attention of the authors and considered for inclusion. This paper showed that the

primary outcome (spontaneous preterm delivery before 37 completed weeks of gestation) was again different from the one that we planned in the meta-analysis, and because the paper was published in 1980, we decided that contacting the author for further information would not be helpful. Both trials included in the meta-analysis were rated as of highest quality according to the Jadad score.[10] The pooled OR of the effect of progesterone in preterm delivery or intrauterine death before 34 weeks' gestation was 1·16 (95% CI 0·89–1·51; figure 2).

	n (events) in progesterone group	n (events) in placebo group	p value*
Mother died	0	0	1·00
Intrauterine death	6	4	0·52
Neonatal death	8	6	0·59
Involved or prolonged inpatient maternal hospital admission	87 (103)	72 (87)	0·16
Involved persistent/significant maternal disability or incapacity	1	0	0·32
Life threatening	1	2	0·56
Chorioamnionitis or intrauterine infection	0	0	1·00
Congenital anomaly or birth defect	0	0	1·00

*p value from exact test.

Table 6: **Safety issues (secondary outcomes)**

	Progesterone		Placebo		Odds ratio progesterone *vs* placebo (95% CI)	p value
	n	Event (%)	n	Event (%)		
Bloating	187	6 (3%)	191	5 (3%)	1·23 (0·37–4·11)	0·73
Fluid retention	187	20 (11%)	191	22 (12%)	0·92 (0·48–1·75)	0·80
Breast tenderness	187	14 (7%)	191	12 (6%)	1·20 (0·54–2·68)	0·64
Excessive weight gain	187	2 (1%)	191	2 (1%)	1·02 (0·14–7·33)	0·98
Nausea	187	10 (5%)	191	22 (12%)	0·43 (0·20–0·94)	0·035
Headache	187	8 (4%)	191	17 (9%)	0·45 (0·19–1·09)	0·077
Dizziness	187	8 (4%)	191	9 (5%)	0·90 (0·34–2·40)	0·84
Difficulty sleeping	187	31 (17%)	191	40 (21%)	0·75 (0·45–1·26)	0·28
Drowsiness	187	8 (4%)	191	4 (2%)	2·09 (0·62–7·06)	0·24
Depression	187	6 (3%)	191	5 (3%)	1·23 (0·37–4·11)	0·73
Itching	187	19 (10%)	191	21 (11%)	0·92 (0·48–1·77)	0·79
Rash	187	7 (4%)	191	4 (2%)	1·82 (0·52–6·32)	0·35
Acne	187	4 (2%)	191	2 (1%)	2·07 (0·37–11·42)	0·41
Excessive hair growth	187	3 (2%)	191	4 (2%)	0·76 (0·17–3·45)	0·73
Hair loss	187	1 (1%)	191	1 (1%)	1·02 (0·06–16·45)	0·99
Jaundice	187	0	191	0	..	..
Allergic reactions	187	1 (1%)	191	1 (1%)	1·02 (0·06–16·45)	0·99
Vaginal irritation	187	20 (11%)	191	15 (8%)	1·45 (0·70–2·83)	0·34
Vaginal itching	187	19 (10%)	191	18 (9%)	1·09 (0·55–2·14)	0·81
Vaginal discharge	187	59 (32%)	191	46 (24%)	1·45 (0·92–2·29)	0·11
Vaginal discomfort	187	24 (13%)	191	17 (9%)	1·51 (0·78–2·91)	0·22
Joint pain	173	11 (6%)	176	13 (7%)	0·85 (0·37–1·96)	0·71
Pubic pain	187	6 (3%)	191	5 (3%)	1·23 (0·37–4·11)	0·73

Data shown are any reported symptom at either of the 6-week or the 10-week visits, without adjustment for the baseline measure.

Table 7: **Maternal symptoms (tertiary outcome)**

Discussion

We have shown that progesterone did not reduce the composite outcome of risk of delivery or intrauterine death before 34 weeks of pregnancy in women with twin pregnancy. Our results accord with the other large published trial[11] in twin pregnancy that used 17-hydroxyprogesterone caproate (250 mg) given intramuscularly from 16–20 to 35 weeks, and with the most recent meta-analysis on this issue.[9] The relative risk of preterm birth or intrauterine death before 35 weeks in the 655 women available for analysis was 1·1 (95% CI 0·9–1·3) in the active compared with the placebo group.[11]

Our study has the following strengths. It was a double-blind, placebo-controlled trial with central randomisation, and it had a prespecified sample size that was achieved, a prespecified primary endpoint and analysis plan that was followed, and a high rate of follow-up. Loss to follow-up for the primary outcome was small. Our exclusion criteria were few, and thus more than four-fifths of women with twin pregnancy were eligible for the study.

Potential limitations of our study are that the uptake of the study in eligible participants was less than we initially anticipated, with only 40% (500/1249) of eligible women agreeing to participate, and that the study was largely undertaken in tertiary referral centres. These issues could have affected the external validity of our trial. The overall rate of preterm delivery or intrauterine death before 34 weeks was 22% (109/494), which is similar to another (singleton) study in which progesterone was shown to be effective.[6] The dose of vaginal progesterone was similar to the dose used in that singleton study,[6] although less than that in another.[8] The dose we used is at the lower end of proven effective doses, but meta-analyses have not shown a dose-response effect.[13] We therefore believe that the dose of progesterone we used was unlikely to have been too small.

Our unexpected observation of overall lower rates of both caesarean section and operative vaginal delivery in the progesterone group should be interpreted with caution. We noted no effect on any other labour parameters and no significant effect when we analysed pre-labour and post-labour caesarean sections separately. The effect on caesarean delivery was not detected in other large studies using progesterone during twin pregnancy (relative risk 1·0, 95% CI 0·9–1·1)[11] or singleton pregnancy (0·94, 0·68–1·30).[7] Progesterone is unlikely to have reduced caesarean section by improving fetal wellbeing, in view of the trend towards increased perinatal mortality that we recorded (14 deaths in the progesterone group *vs* ten in the placebo group). Furthermore, progesterone was unlikely to have improved uterine contractility during labour since it is known to have a relaxant, rather than a stimulatory, effect on the

	Progesterone	Placebo	Odds ratio progesterone *vs* placebo (95% CI)	p value
How satisfied were you with your study treatment overall? (1=very satisfied; 10=completely dissatisfied)	2·8 (2·1)	2·8 (1·9)	0·0 (0·5 to 0·4)	0·89
Do you think your study treatment worked? (1=yes, worked perfectly; 10=no, did not work at all)	3·8 (2·3)	3·9 (2·5)	–0·1 (0·6 to 0·4)	0·73
How easy was your treatment to use overall? (1=very easy; 10=very difficult)	2·6 (1·9)	2·5 (1·7)	0·2 (–0·2 to 0·6)	0·38
How easy was your treatment to insert? (1=very easy; 10=very difficult)	2·6 (1·9)	2·4 (1·7)	0·2 (–0·2 to 0·6)	0·30
How easy was your treatment to remember to use? (1=very easy; 10=very difficult)	2·6 (1·7)	2·9 (1·7)	–0·2 (–0·6 to 0·2)	0·26
How pleasant was your treatment to use? (1=very pleasant; 10=very unpleasant)	4·8 (2·0)	4·9 (1·8)	–0·1 (–0·5 to 0·3)	0·60
How messy was your treatment to use? (1=very messy; 10=not at all messy)	5·5 (2·5)	6·1 (2·4)	–0·6 (–1·1 to 0·1)	0·026
How uncomfortable was your treatment to use? (1=very uncomfortable; 10=very comfortable)	6·4 (2·5)	6·5 (2·3)	–0·1 (–0·6 to 0·4)	0·65
Were there many side-effects of the study treatment overall? (1=a lot of side-effects; 10=no side-effects)	8·2 (2·3)	8·4 (1·9)	–0·2 (–0·7 to 0·2)	0·32
An alternative to gel would be an intramuscular injection once per week. If this injection were only a bit uncomfortable, which would you prefer? (1=daily vaginal gel; 10=weekly injection)	4·3 (3·6)	4·2 (3·6)	0·2 (–0·6 to 0·9)	0·70
If this injection was quite uncomfortable, which would you prefer? (1=daily vaginal gel; 10=weekly injection)	3·3 (3·0)	3·1 (2·9)	0·2 (–0·4 to 0·9)	0·50
Overall, how satisfied were you with participating in the STOPPIT study? (1=very satisfied; 10=completely dissatisfied)	2·5 (2·2)	2·1 (1·6)	0·4 (–0·1 to 0·8)	0·093

Data are mean (SD) over two visits (at weeks 6 and 10), adjusted for the baseline measure.

Table 8: **Maternal satisfaction (tertiary outcome)**

uterus.[14] Because reduction in caesarean section is one of several secondary outcomes in our study, and because of the absence of biological plausibility and no confirmation from other studies, we believe that this finding is most likely to be one of chance.

The clinical implication of our study is that progestogens are not effective in women with twin pregnancy for prevention of preterm delivery. Although six further clinical trials of the effect of 17-hydroxyprogesterone caproate or progesterone in the prevention of preterm delivery in twin pregnancy are ongoing—two large trials (registration numbers NCT00329914 [with a planned sample size of 750] and ISRCTN40512715 [with a planned sample size of 660]) and four smaller trials (NCT00343265, NCT00480402, NCT00141908, and NCT 00163020, with a combined planned sample size of 957)—unless their combined effect size is large with an odds ratio of 0·65 or less, they will not change the overall conclusion of this and the previous[11] study that progesterone is ineffective.

Our results contrast with the randomised trials and meta-analyses of high-risk singleton pregnancies in which progesterone seems to be effective in reducing preterm birth, although this reduction will only be clinically useful if accompanied by long-term improvement in the health of offspring. At present, there is no evidence to suggest that this is the case. This issue is being specifically addressed in singletons in a randomised trial of progesterone, with infant function at 2–3 years of age as our primary outcome (OPPTIMUM study, registration number ISRCTN14568373). The biological mechanism by which preterm delivery occurs might be different in twin and singleton pregnancy, and this hypothesis merits further study. Perhaps stretching of uterine muscle has a substantial role in preterm labour in twin pregnancy, and infection and inflammation a role in singletons. We did not recruit women with higher multiple pregnancy (eg, triplets), but a recent publication did not show any effect of progesterone in prevention of preterm birth in triplet pregnancy.[15]

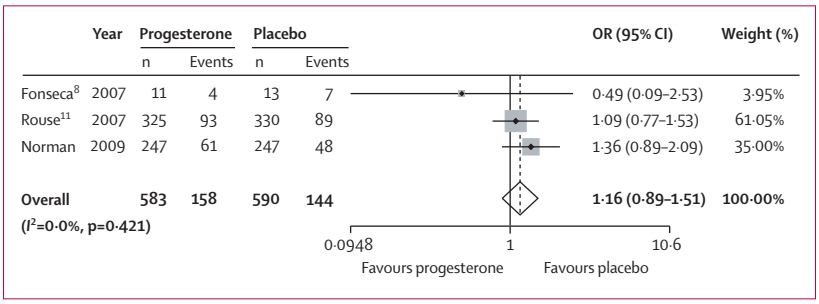

Figure 2: **Meta-analysis of the effect of progesterone in prevention of preterm delivery before 34 weeks' duration**

The figure shows the odds ratio for each study as a square (with size proportional to the amount of information) and the horizontal line depicts the 95% CIs. The open diamond indicates the odds ratio (OR) with 95% CI overall. The vertical line, at the odds ratio of unity, corresponds to the line of no effect.

Contributors

JEN and FM conceived the study. JEN, FM, PO, HM, KH, SC, AAC, GM, PD, SS, and JN designed the study. JEN, FM, PO, HM, KH, SC, AAC, GM, PD, SS, GT, ST, BM, and JGT acquired the data. GMacL and JN analysed the data. JEN drafted the article. JPN was chair of the Data Safety and Monitoring Board. All authors interpreted the data, revised the Article critically for important intellectual content, and approved the final version.

Conflicts of interest

JEN and ST have received grants from government and charitable organisations for research into understanding the mechanism of term and preterm labour and investigating treatments. JEN has acted as a consultant to a small drug company that was considering developing treatments for preterm labour. Additionally, she is named as an inventor on patent applications for two compounds potentially useful in preterm labour prevention. ST has acted as a consultant to the pharmaceutical industry. JPN was chair of the Data Safety and Monitoring Board. All other authors declare that they have no conflicts of interest.

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